Faculty Disclosures

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Learning Objectives

At the end of this presentation, participants will be better able to:
- Discuss when migraine prevention should be considered
- Identify the principles and objectives of therapy for migraine prevention
- Distinguish between medication overuse and medication overuse headache (MOH)
- Recall the factors that determine drug choice in migraine prevention
- Remember which evidence-based preventive migraine treatments are currently supported by evidence from randomized, controlled clinical trials
- Educate patients about the rationale for migraine prevention and the options available for treatment
Nearly 40% of Patients Should be Offered or Considered for Migraine Preventive Therapy


Goals of Preventive Treatment

- Decrease
  - Migraine days
  - Headache days
  - Intensity of symptoms
  - Duration of attacks
  - Disability

- Improve
  - Response to acute medications
  - Functional ability

Prevent disease progression

Benefits occur over time


General Principles of Migraine Prevention

- Start with low dose and increase slowly
- Allow for an adequate trial (2–3 months)
- Monitor medication usage
  - Avoid overuse of acute medications
  - Limit/Eliminate interfering drugs
- Evaluate preventive therapy
  - Use calendar/diary
  - Taper/discontinue if well-controlled at 6 months

General Principles of Migraine Prevention cont.

- Manage communications
  - Ask about patient preference
  - Discuss contraception
- Optimize medication use
  - Best efficacy
  - Fewest AEs

Consider Comorbid Conditions

Cardiovascular
- Heart attack/angina
- Mitral valve prolapse
- Hypertension/hypotension
- Stroke
- Raynaud’s syndrome
  - PFO (with aura)

GI disorders
- Ulcer disease
- Colitis
- IBS

Mood disorders
- Depression
- Mania
- Anxiety
- Panic

Allergy/Asthma

Migraine

CNS
- Epilepsy
- Essential tremor
Consider Prevention When...

- Significantly interferes with routine activities despite use of acute treatment
- Attack frequency exceeds 1 per week
- Elevated risk of:
  - Medication overuse
  - Chronic Daily Headache

Consider Prevention When... cont.

- Acute medications
  - Ineffective
  - Contraindicated
  - Troublesome AEs
  - Overused
- Patients express/acknowledge a preference
- Uncommon migraine subtypes are present
  - Hemiplectic
  - Basilar
  - Prolonged Aura
  - Migrainous Infarction

Lifestyle Modifications

- Inquire about sleep disturbances/sleep hygiene
  - Avoid too little sleep, daytime naps
  - Avoid oversleeping in the morning
- Explain how to avoid excessive fatigue by pacing activities during the day/week
- Reduce and manage stress
- Encourage regular meals and exercise
- Behavioral therapy

Spierings EL et al. Headache. 2001 April; 41:554-558.
Behavioral Therapy for Episodic and Chronic Migraine

Benefits may include:
- Reduction in headache severity, frequency, and headache-related disability
- Reduction in reliance on drugs
- Enhanced HRQoL and sense of control

Cognitive behavioral therapy

Factors in Preventive Drug Selection

Evidence-based Guidelines for Prevention of Migraine
Evidence of Efficacy

- Guidelines exist for episodic
- Most evidence for prevention of episodic migraine
- Prevention of CM
  - Botulinum toxin
  - Topiramate

Preventive Therapies: Level A

- Divalproex sodium
- Sodium valproate
- Topiramate
- Metoprolol
- Cognitive Behavioral Therapy
- Timolol
- Butterbur
- Biofeedback
- Relaxation
- Training

Preventive Therapies: Level B

- Amitriptyline
- Venlafaxine
- Atenolol
- Nadolol
- NSAIDs
  - Fenoprofen
  - Ibufrofen
  - Ketoprofen
  - Naproxen
- Riboflavin
- Magnesium
- Mig 99 (feverfew extract)
- Histamine (subcutaneous)

Preventive Therapies: Level C

- Possibly effective and may be considered for migraine prevention
  - Pindolol
  - Nebivolol
  - Carbamazepine
  - Guanfacine
  - Candesartan
  - Lisinopril

Preventive Therapies: Level U

- Evidence is conflicting or inadequate to support or refute use for migraine prevention
  - Gabapentin
  - Fluoxetine
  - Fluvoxamine
  - Protriptyline
  - Acenocoumarol
  - Courmadin
  - Picotamide
  - Bisoprolol
  - Nicardipine
  - Nifedipine
  - Nimodipine
  - Verapamil
  - Acetazolamide
  - Cyclandelate
  - Aspirin
  - Indomethacin
  - Omega 3
  - Hyperbaric oxygen
  - Estrogen
  - Co-Q10

Preventive Therapies: Level A, B, and C Negative

<table>
<thead>
<tr>
<th>Level</th>
<th>Guidance for migraine prevention</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Negative</td>
<td>Ineffective; should not be offered</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>B Negative</td>
<td>Probably ineffective; should not be considered</td>
<td>Clomipramine Montelukast</td>
</tr>
<tr>
<td>C Negative</td>
<td>Possibly ineffective; may not be considered</td>
<td>Acebutolol Glonazepam Nabumetone Ocrelizumab Telmisartan</td>
</tr>
</tbody>
</table>

### Evidence-based Preventive Therapies: Limitations and Opportunities

<table>
<thead>
<tr>
<th>Medication</th>
<th>Contraindication(s)</th>
<th>Coexisting condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Liver disease</td>
<td>Mania</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Kidney stones</td>
<td>Epilepsy, Anxiety</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>Mania</td>
<td>Other pain disorders</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Mania</td>
<td>Depression</td>
</tr>
</tbody>
</table>

**Note:** TCA, Tricyclic antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor

### Evidence-based Preventive Therapies: Limitations and Opportunities cont.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Contraindication(s)</th>
<th>Coexisting condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Asthma</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Depression</td>
<td>Angina</td>
</tr>
<tr>
<td>Timolol</td>
<td>Raynaud’s</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil (with aura)</td>
<td>Constipation</td>
<td>Migraine with aura</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angina</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>Ulcer disease</td>
<td>Arthritis</td>
</tr>
<tr>
<td></td>
<td>Gastritis</td>
<td>Other pain disorders</td>
</tr>
<tr>
<td><strong>Complementary</strong></td>
<td></td>
<td>Preference for natural products</td>
</tr>
<tr>
<td>Riboflavin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-Q10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petasites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butterbur</td>
<td></td>
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</tr>
</tbody>
</table>

### Preventive Treatment ARS Question 1

All of the following are general principles in migraine prevention except:

A. Discuss contraception
B. Consider comorbid conditions
C. Allow for a 1-month trial
D. Low initial dose, titrate slowly
Prevention of Chronic Migraine (CM)

General Principles in CM Prevention

<table>
<thead>
<tr>
<th>Principle</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individualize medication selection</td>
<td>Few patients:</td>
</tr>
<tr>
<td></td>
<td>• Receive preventive therapy</td>
</tr>
<tr>
<td></td>
<td>• Comply with treatment within first 3 months</td>
</tr>
<tr>
<td></td>
<td>• Continue treatment for 1 year</td>
</tr>
<tr>
<td>Consider comorbid and coexistent illness/disorders</td>
<td>Maximize therapeutic opportunities</td>
</tr>
<tr>
<td></td>
<td>• Choose a single drug for both conditions when possible</td>
</tr>
<tr>
<td></td>
<td>• Combine preventive drugs in appropriate cases</td>
</tr>
</tbody>
</table>


General Principles in CM Prevention cont.

Select Medicines Based on Evidence in CM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Double-blind placebo-controlled trials in CM</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>One double-blind, placebo-controlled trial in chronic daily headache</td>
</tr>
<tr>
<td>Valproate</td>
<td>Small placebo-controlled and comparator trials in CM</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Small open-label trial in transformed migraine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Small double-blind, placebo-controlled trial in chronic daily headache</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Small double-blind, placebo-controlled trial in chronic daily headache (adjunctive)</td>
</tr>
<tr>
<td>Neurotoxins</td>
<td></td>
</tr>
<tr>
<td>OnabotulinumtoxinA*</td>
<td>Double-blind placebo-controlled trials in CM</td>
</tr>
</tbody>
</table>

*FDA approved for CM
General Principles in CM Prevention cont.

**Medication Overuse**
- Overuse of acute medications is common
- 50%–80% of CM patients seen in headache clinics overuse acute medications
- Not all CM patients overuse medications
- Important clinical distinction:
  - Activity: overuse of medications
  - Disorder: Medication Overuse Headache (MOH)

ICHD-III β MOH

**New Diagnostic Criteria**

A. Headache* ≥15 days/month in a patient with pre-existing headache disorder

B. Regular overuse for >3 months of ≥1 acute/symptomatic treatment
   1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days/month
   2. Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on ≥15 days/month on a regular basis without overuse of any single class alone

*If attributed to substance withdrawal, sub-classify as caffeine withdrawal headache; opioid withdrawal headache; estrogen withdrawal headache

Comparing MOH with CM

<table>
<thead>
<tr>
<th>MOH</th>
<th>CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Headache* ≥15 days/month in a patient with pre-existing headache disorder</td>
<td></td>
</tr>
<tr>
<td>B. Regular overuse for &gt;3 months of ≥1 acute/symptomatic treatment</td>
<td></td>
</tr>
</tbody>
</table>
  1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 days/month
  2. Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on ≥15 days/month on a regular basis without overuse of any single class alone |
| A. Headache (tension-type-like and/or migraine-like) on 15 days/month for >3 months |
| B. Patient has had ≥5 attacks fulfilling criteria for migraine with and/or without aura |
| C. On 8 days/month for >3 months, attacks fulfilling criteria for migraine with or without aura or believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative |

CM and MOH can co-exist

Treatment of MOH

- Medication Overuse
  - Preventive Therapy
    - Detoxification
    - Fail
      - Fail

Topiramate Reduces Migraine Days in CM

- Mean decrease in migraine days/month (week 12-16)
  - Topiramate n=32
  - Placebo n=27

- Treatments
  - Topiramate 100 mg/day
    (50–200 mg/day allowed)
  - Placebo

- Subjects: 78% met the definition for acute medication overdose at baseline

- p<0.05 vs placebo

Better Long-term Outcomes in MOH with Preventive Treatment Plus Withdrawal

- Patients withdrew from either topiramate or a placebo
- Percent of patients with ≥50% reduction in migraine

- p<0.05 vs placebo

Topiramate is Effective in CM Patients with or without Medication Overuse

![Graph showing similar reductions in mean migraine days/month.](image1)

OnabotulinumtoxinA Significantly Outperforms Placebo from 4–24 Weeks in CM

![Graph showing mean decrease in cumulative hours of headache on headache days.](image2)

OnabotulinumtoxinA: Pooled Efficacy at Week 24

<table>
<thead>
<tr>
<th>Mean Change From Baseline</th>
<th>OnabotulinumtoxinA (n=88)</th>
<th>Placebo (n=96)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days*</td>
<td>-8.4</td>
<td>-6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative headache hours on headache days</td>
<td>-119.7</td>
<td>-80.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Patients with severe (B6) HT-6 score</td>
<td>67.6</td>
<td>78.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Frequency of migraine episodes</td>
<td>-4.9</td>
<td>-4.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Frequency of acute headache medication intake</td>
<td>-10.1</td>
<td>-9.4</td>
<td>0.247</td>
</tr>
</tbody>
</table>

*Primary Measure

Preventive Treatment ARS Question 2

At least _____% of CM patients seen in headache clinics overuse acute medications.

A. 30
B. 50
C. 78
D. 90

What’s New in Migraine Prevention?

CGRP Monoclonal Antibodies
- Inhibition of neurogenic vasodilation with a long duration of action
- Skin vasodilation or increase in MMD diameter similar to CGRP receptor antagonists but slower onset
- Inhibition still evident one week after dosing
- Chronic treatment: no detectable effects on heart rate or blood pressure

Neurostimulation
- Nerves
  - Vagal
  - Frontal
- Transcranial magnetic stimulation
- Sphenopalatine ganglion stimulation

1. Exclude Secondary Headache
   - Complete history and examination
   - Screen for red flags: SNOOP
     - Yes
   - Evaluate for Secondary Headache

2. Identify Primary Headache Syndrome
   - Episodic
     - Short Duration ≤ 4 hours
     - Long Duration > 4 hours
   - Chronic
     - Short Duration ≤ 4 hours
     - Long Duration > 4 hours

3. Diagnose Specific Headache Disorder
   - Migraine
     - Probable Migraine
     - Tension-type
   - Chronic Migraine
     - Chronic Tension-Type
     - New Daily Persistent Headache
     - Hemiparesis Continua
   - Medication overuse?
     - Yes
Summary

The most important aspects of the preventive treatment of migraine include:

• Accurate diagnosis
• Nonpharmacotherapy
  – Trigger management
  – Lifestyle modification
  – Behavioral therapy
• Use of symptomatic and prophylactic medications
• Management of medication overuse
• Monitor response to treatment: Diary, HIT-6, MSQOL
• Meaningful communication with/education of patients